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| 10/719,913 | 11/21/2003 | Gary A. Dahl | EPICEN-09580 | 3340 |
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| Casimir Jones, S.C. 2275 DEMING WAY, SUITE 310 MIDDLETON, WI 53562 | | | STAPLES, MARK | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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|------------------------------|--------------------------------------|------------------------------------|
| Office Action Summary | Application No. 10/719,913 | Applicant(s) DAHL ET AL. |
| | Examiner MARK STAPLES | Art Unit 1637 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 21 December 2009.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 7-40 is/are pending in the application.
- 4a) Of the above claim(s) 8, 9, 11-15, 31-35, and 39 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 7,10,16-30,36-38 and 40 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date _____
- 4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date _____
- 5) Notice of Informal Patent Application
- 6) Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/21/2009 has been entered.

2. Applicant's amendment of claims 7, 17, 26, 30, 32, 34, 35, 36 and 39 in the paper filed on 12/21/2009 is acknowledged.

Claims 7, 10, 16-30, 36-38, and 40 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Affidavit

3. The Declaration under 37 CFR 1.132 filed 12/21/2009 is sufficient to overcome the rejection of claim 7, 10, 16-30, 36-38, and 40 based upon Soares et al. (1998) under 35 U.S.C. 103(a).

It is noted that Applicant also argues that none of the steps of the instantly claimed methods were used in the methods of Lorincz et al. Examiner disagrees and

as noted in the rejections below, Lorincz et al. teach the steps of the instant methods. Applicant also argues that Lorincz et al. do not specifically teach the claimed sense promoter primer. However this argument is moot in view of the newly cited teachings of Christina et al., as given below.

Rejections that are Withdrawn

Claim Rejections Withdrawn - 35 USC § 103(a)

4. The rejection of claims 7, 10, 16-24, 26, 28, 30, 36, 38, and 40 under 35 U.S.C. 103(a) as being unpatentable over Soares et al. (United States Patent 5,830,662 issued November 3, 1998) and Lorincz et al. (US Patent No. 6,136,535, issued Feb. 2000, previously cited) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

5. The rejection of claims 25, 27, 29, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soares et al. and Lorincz et al. as applied to claims 26 and 36 above, and further in view of Hall et al. (US Patent No. 5,994,069, issued 1999, previously cited) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

New Rejections

New Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 7, 10, 16-24, 26, 28, 30, 36, 38, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christian et al. (published online No. 27, 2001), Lizardi et al. (United States Patent 6,316,229 issued November 13, 2001), and Lorincz et al. (US Patent No. 6,136,535, issued Feb. 2000, previously cited).

Regarding claims 7 and 30, Christian et al. teach methods for making a transcription products corresponding to a target nucleic acid sequence in a target

nucleic acid in a sample (entire publication, especially the Abstract), the method comprising the steps of:

- (1) primer extending a sense promoter primer to generate a sense promoter-containing first- strand DNA using a target nucleic acid as a template, the sense promoter primer comprising a 5'-end portion that exhibits a sense RNA polymerase promoter sequence and a 3'-end portion that exhibits a sequence complementary to the 3'-end of the target sequence (See Figure 1 and the entire text on p. 14238);
- (2) ligating the 5' and 3' ends of the sense promoter-containing first-strand DNA to each other to obtain a single-stranded circular sense promoter-containing first-strand DNA (see 1st sentence of the 2nd column on p. 14239 and see Figure 1);
- (3) annealing an anti-sense promoter oligonucleotide to the sense promoter sequence in the sense promoter containing first-strand DNA to obtain a transcription substrate (see 1st sentence of the 2nd column on p. 14239 noting that both a sense and and see Figure 1); and
- (4) transcribing the transcription substrate to make a transcription products corresponding to the target nucleic acid sequence (see last sentence of Abstract).

Regarding claims 7 and 30, Christian et al. teach DNA and teach transcribing mRNA and thus suggest but do not specifically teach transcribing cDNA transcription substrates.

Regarding claims 7, 10, 16-22, 24, 28, 30, 36, 38, and 40, Lorincz et al. (Feb. 2000) teach a method comprising the steps of:

- (1) obtaining said target nucleic acid (see Figure 1A and see claim 1 or 7 where the target nucleic acids may be a sample; see column 17 lines 14-16: "This process is capable of analyzing multiple samples sequentially or simultaneously"; and see column 3 lines 15 and 16: "Any nucleic acid may be amplified by the method of the present invention");
- (2) obtaining said sense promoter primer, the sense promoter primer comprising a 5'-end portion comprising a sense transcription promoter, the sense promoter primer comprising a 5'-end portion that exhibits a sense RNA polymerase promoter sequence (see column 2 lines 56-63), and a 3'-end portion that is complementary to the target (see Figure 1A and see claim 1 or 7);
- (3) annealing [hybridizing] the sense promoter primer with the target nucleic acid so as to form a target nucleic acid-sense promoter primer complex (see Figure 1A and see claim 1 or 7);
- (4) contacting the target nucleic acid-sense promoter primer complex with a polymerase under polymerization reaction conditions to obtain first-strand nucleic acid that is complementary to the target sequence (see Figure 1A and see claims 1 and 6, or 7 and 11);
- (5) ligating the first-strand nucleic acid to itself under ligation conditions so as to obtain circular sense promoter-containing first-strand nucleic acid (see column 4 lines 3 and 4: 11);

"Optionally, a ligation reaction may be carried out to fill the gap between the promoter and the template");

(6) obtaining an anti-sense promoter oligonucleotide (see Figure 4 and the circle T7 oligo given there and note that this anti sense promoter is attached to and antibody which an analyte binding substance, ABS);

(7) annealing the anti-sense promoter oligonucleotide to the circular sense promoter-containing first-strand nucleic to obtain a circular transcription substrate (see Figure 4); and

(8) contacting the circular transcription substrate with an RNA polymerase under transcription conditions wherein a transcription product is obtained (see Figure 4 for amplification of the circular substrate with polymerase to obtain additional product. And for use of an RNA polymerase see column 3 lines 54-57: "This product is subjected to transcription using, for example, RNA polymerase. In this way, a template DNA [transcription substrate] can be indirectly amplified without the need to carry out any cycled reaction").

Regarding claims 16 and 17, Lorincz et al. (Feb. 2000) teach a method using a wild type T7 RNA polymerase (see column 11, lines 23-25).

Regarding claim 18, Lorincz et al. (Feb. 2000) teach a method using four dNTPs (dATP, dGTP, dCTP, dTTP) four NTPs (ATP, GTP, CTP, UTP), see column 23, lines 17-20.

Regarding claim 19, Lorincz et al. (Feb. 2000) teach an *in vitro* method (see column 2 lines 61-64).

Regarding claim 22, Lorincz et al. (Feb. 2000) teach a method using messenger RNA, mRNA (see column 5 lines 7).

Regarding claims 23 and 40, Lorincz et al. (Feb. 2000) teach a synthetic promoter (see Example 1 for synthetic promoter-primer).

Regarding claim 24, Lorincz et al. (Feb. 2000) teach a target specific sequence (see claim 1).

Regarding claim 26 and 30, Lorincz et al. (Feb. 2000) teach a method for amplifying the amount of a template-complementary product, the method comprising the steps of:

- (1) obtaining a transcription product (see Figure 1A and see claim 1 or 7; see column 3 lines 15 and 16: "Any nucleic acid may be amplified by the method of the present invention"; and see column 6 lines 23 and 24: "generating multiple RNA transcripts", nucleic acids, which are transcription products);
- (2) obtaining a sense promoter primer comprising a 3'-end portion that is complementary to the 3'-end of the transcription product (see Figure 1A and see claim 1 or 7;);
- (3) annealing [hybridizing] the sense promoter primer to the transcription product (see Figure 1A and see claim 1 or 7);

(4) primer-extending the sense promoter primer annealed to the transcription product acid with a DNA polymerase under DNA synthesis conditions to obtain first-strand cDNA (see Figure 1A and see claims 1 and 6, or 7 and 11; see column 3 lines 15 and 16: "Any nucleic acid may be amplified by the method of the present invention"; and see column 13 line 30-32: "Transcripts may also be subjected to a reverse transcriptase reaction in order to generate cDNAs . . . ");

(5) ligating the first-strand cDNA, wherein the 5'-end is covalently joined to the 3'-end of the first-strand cDNA to obtain circular sense promoter-containing first-strand DNA (see column 4 lines 3 and 4: "Optionally, a ligation reaction may be carried out to fill the gap between the promoter and the template");

(6) annealing an anti-sense promoter oligonucleotide to the circular sense promoter-containing first-strand cDNA to obtain a circular substrate for transcription (see Figure 4 for circle T7 oligo); and

(7) contacting the circular substrate for amplification with a RNA polymerase under conditions to obtain additional transcription product (see Figure 4 for amplification of the circular substrate with polymerase to obtain additional product).

Regarding claims 28 and 38, Lorincz et al. (Feb. 2000) teach a wash step that removes the RNA hybrid (annealed RNA) from other components (see Example 2, especially line 38).

Regarding claims 36, Lorincz et al. (Feb. 2000) teach a method for amplifying an amount of template-complementary transcription product, the method comprising:

- (1) obtaining a transcription product by transcription of a template of a probe that is complexed with an analyte binding substance-oligo (see Figure 4 and claims 7, 10, 13, and 16; see column 3 lines 15 and 16: "Any nucleic acid may be amplified by the method of the present invention"; and see column 6 lines 23 and 24: "generating multiple RNA transcripts", nucleic acids, which are transcription products);
- (2) obtaining a sense promoter primer comprising a 3'-end portion that is complementary to the 3'-end of the transcription product (see Figure 4 and claims 7 10, 13, and 16);
- (3) annealing the sense promoter primer to the transcription product;
- (4) primer-extending the promoter primer annealed to the transcription product with an RNA-dependent DNA polymerase under DNA synthesis conditions so as to obtain first-strand cDNA (see column 13 lines 9-11: "Transcripts may also be subjected to a reverse transcriptase reaction in order to generate cDNAs which may be analyzed");
- (5) ligating the first-strand cDNA, wherein the 5'-end is covalently joined to the 3'-end of the first-strand cDNA so as to obtain circular sense promoter-containing first-strand cDNA (see column 4 lines 3 and 4: "Optionally, a ligation reaction may be carried out to fill the gap between the promoter and the template");

- (6) annealing an anti-sense promoter oligo to the circular sense promoter-containing first-strand cDNA so as to obtain a circular substrate for transcription (see Figure 4 and the circle T7 oligo given there);
- (7) contacting the circular substrate for transcription with an RNA polymerase under transcription conditions so as to obtain additional transcription product; and
- (8) obtaining the additional transcription product (for claims 7 and 8 see Figure 4 for amplification of the circular substrate with polymerase to obtain additional product. And for use of an RNA polymerase see column 3 lines 54-57: "This product is subjected to transcription using, for example, RNA polymerase. In this way, a template DNA [transcription substrate] can be indirectly amplified without the need to carry out any cycled reaction").

Regarding claims 7, 26, 30, and 36, Lorincz et al. (Feb. 2000) teach circular cDNA which is partially single-stranded (that is circular cDNA which is a duplex of single and double strands), but do not specifically teach circular cDNA which is completely single-stranded. Lorincz et al. teach sense promoter primers and suggest but do not specifically

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Lorincz et al. by using the sense promoter primer as suggested by Christian et al. with a reasonable expectation of success. The motivation to do so is provided by Christian et al. who

teach that use of sense promoter primers in rolling circle amplification improves efficiency in detection of gene copy number and single base mutations up to 90% (see Abstract). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Regarding claim 7, Lizardi et al. teach methods for making a transcription products corresponding to a target nucleic acid sequence in a target nucleic acid in a sample (entire patent), the method comprising the steps of:

- (1) primer extending an anti-sense promoter primer to generate a sense promoter-containing first- strand cDNA using a target nucleic acid as a template(see column 69 lines 42-44);
- (2) ligating the 5' and 3' ends of the sense promoter-containing first-strand cDNA to each other to obtain a single-stranded circular sense promoter-containing first-strand cDNA (see first two sentences of the Abstract);
- (3) annealing/hybridizing an anti-sense promoter oligonucleotide to the sense promoter sequence in the sense promoter containing first-strand cDNA to obtain a transcription substrate (see 3rd sentences of the Abstract);; and
- (4) transcribing the transcription substrate to make a transcription products corresponding to the target nucleic acid sequence (see Figure 8 and see column 18 lines 29-66).

Regarding claim 7, Lizardi et al. do not specifically teach a sense promoter primer

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of Christien and Lorincz et al. by transcribing the transcription substrate to make a transcription product as suggested by Lizardi et al. with a reasonable expectation of success. The motivation to do so is provided by Lizardi et al. who teach that cDNA is transcribed into RNA for their disclosed primer extension sequencing procedures and allows for discrimination between two or more forms of the target sequence that differ at a particular nucleotide (see column 69 lines 42-44 and see column 66 lines 46-54). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

9. Claims 25, 27, 29, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Christian et al., Lizardi et al., and Lorincz et al. as applied to claims 26 and 36 above, and further in view of Hall et al. (US Patent No. 5,994,069, issued 1999, previously cited).

Christian et al., Lizardi et al., and Lorincz et al. teach as noted above and teach a 3' end labeled phosphate labeled promoter primer, which is a synthetic primer promoter.

Christian et al., Lizardi et al., and Lorincz et al. do not specifically teach a promoter primer comprising a phosphate group on its 5' end.

Hall et al. (1999) teach labeling the 5' end (see claims 9 and 12).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Christian et al., Lizardi et al. by labeling, instead of the 3'end, the 5' end of a oligonucleotide promoter primer with a phosphate group as suggested by Hall et al. with a reasonable expectation of success. The motivation to do so is provided by Hall et al. who teach the successful detection of oligonucleotides which are labeled on the 5' end. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

10. No claim is free of the prior art.
11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark Staples/
Primary Examiner, Art Unit 1637
January 13, 2010